PCT

REC'D 1 1 JAN 2002

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant'	s or ag	ent's file reference		See Notification of Transmittal of International	
05213-0551 WP			FOR FURTHER ACTION	Preliminary Examination Report (Form PCT/IPEA/416)	
International application No.			International filing date (day/mon	nth/year) Priority date (day/month/year)	
PCT/US00/25166 14			14/09/2000	14/09/1999	
Internation C12N15		ent Classification (IPC) or	national classification and IPC		
Applicant		,			
ENTRE	MED,	INC. et al.			
1. This and i	intern s tran	ational preliminary exa smitted to the applican	mination report has been prepare t according to Article 36.	ed by this International Preliminary Examining Authority	
2. This REPORT consists of a total of 7 sheets, including this cover sheet.					
This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.					
3. This	report	contains indications re	elating to the following items:		
1	\boxtimes	Basis of the report			
11	\boxtimes	Priority			
Ш		Non-establishment of	opinion with regard to novelty, in	nventive step and industrial applicability	
IV	×	Lack of unity of inven	tion		
V	×		under Article 35(2) with regard to tions suporting such statement	o novelty, inventive step or industrial applicability;	
VI		Certain documents of	ited		
VII	\boxtimes	Certain defects in the	international application		
VIII		Certain observations	on the international application		
Date of sub	missio	n of the demand	Date of	f completion of this report	
16/04/20	16/04/2001			2002	
		address of the internation	nal Authoria	ized officer	
European Patent Office D-80298 Munich			Nicho	giannopoulou, A	
Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465			•	one No. +49 89 2399 8054	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/25166

I. Basis of the report

1.	the an	With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): Description, pages:				
	1-5	56	as originally filed			
	Cla	aims, No.:				
	1-2	23	as originally filed			
	Drawings, sheets:					
	1/5	-5/5	as originally filed			
	Se	quence listing part	t of the description, pages:			
	1-8	, filed with the letter	of 19.12.2000			
2.	With regard to the language , all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.					
	The	ese elements were a	available or furnished to this Authority in the following language: , which is:			
		the language of a	translation furnished for the purposes of the international search (under Rule 23.1(b)).			
		the language of pu	ublication of the international application (under Rule 48.3(b)).			
		the language of a 55.2 and/or 55.3).	translation furnished for the purposes of international preliminary examination (under Rule			
3.			eleotide and/or amino acid sequence disclosed in the international application, the y examination was carried out on the basis of the sequence listing:			
		contained in the in	ternational application in written form.			
		filed together with the international application in computer readable form.				
			ently to this Authority in written form.			
	\boxtimes	furnished subsequently to this Authority in computer readable form.				
	Ø	The statement that the subsequently furnished written sequence listing does not go beyond the disclosure the international application as filed has been furnished.				
	×	The statement that listing has been fur	t the information recorded in computer readable form is identical to the written sequence rnished.			

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/25166

		the description,	pages:						
		the claims,	Nos.:						
		the drawings,	sheets:						
5	. 🗆	This report has been considered to go be	n established as if (some of) the amendments had not been made, since they have been yond the disclosure as filed (Rule 70.2(c)):						
		(Any replacement sh report.)	neet containing such amendments must be referred to under item 1 and annexed to this						
6.	Ad	ditional observations, if necessary:							
II.	Pri	Priority							
1.		☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:							
		☐ copy of the earli	er application whose priority has been claimed.						
		☐ translation of the	e earlier application whose priority has been claimed.						
2.		This report has been been found invalid.	established as if no priority had been claimed due to the fact that the priority claim has						
		Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.							
3.		dditional observations, if necessary: ee separate sheet							
IV	. Lac	k of unity of invention	on.						
1.	In r	esponse to the invitation	on to restrict or pay additional fees the applicant has:						
		restricted the claims.							
		paid additional fees.							
		paid additional fees u	nder protest.						
		neither restricted nor	paid additional fees.						
2.		This Authority found to 68.1, not to invite the	hat the requirement of unity of invention is not complied and chose, according to Rule applicant to restrict or pay additional fees.						
3.	This	Authority considers th	nat the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is						
		complied with.							

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/25166

		not complied with for th	e follow	ing reaso	ons:		
4.	. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:						
	×	all parts.					
		the parts relating to claim	ms Nos				
	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement Statement						
	Nov	velty (N)	Yes: No:	Claims Claims	· · · - ·		
	Inve	entive step (IS)	Yes: No:		=5		
	Indu	ustrial applicability (IA)	Yes: No:	Claims Claims	1-23		

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

Re Item II

Priority

1. The present application validly claims priority from 14.09.1999. Any documents cited in the International Search Report as P documents have therefore not been considered as comprised in the prior art relevant for the present application.

Re Item IV

Lack of unity of invention

1. The present application relates to processes for the recombinant production (claims 1-10) and purification (claims 11-23) of Endostatin™. Since both Endostatin™ as well as its recombinant production are well known from the prior art (see D below), there is no special technical feature, i.e. a contribution each of these processes makes over the prior art, unifying them into a single invention. The IPEA therefore agrees with the objection put forward by the ISA as to lack of unity pursuant to Rule 13 PCT, and considers that the present application relates to two distinct groups of inventions. However, since all claims could be searched without effort justifying additional fees. the two inventions will be examined jointly without requirement of additional examination fees. Should the application enter the European phase, an objection under the corresponding EPC article will be raised.

EXAMINATION REPORT - SEPARATE SHEET

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1. Reference is made to the following documents:
 - D1: WO 99 26480 A (GENETIX PHARMACEUTICALS INC; MASSACHUSETTS INST TECHNOLOGY (US)) 3 June 1999 (1999-06-03)
 - JOHN H ET AL: 'Novel glycosylated forms of human plasma endostatin and D2: circulating endostatin-related fragments of collagen XV.' BIOCHEMISTRY, vol. 38, no. 32, 10 August 1999 (1999-08-10), pages 10217-10224, XP002162137
 - D3: DHANABAL M ET AL: 'Endostatin: Yeast production, mutants, and antitumor effect in renal cell carcinoma' CANCER RESEARCH, vol. 59, no. 1, 1999. pages 189-197, XP002100110
 - D4: BOEHM T ET AL: 'Zinc-binding of endostatin is essential for its antiangiogenic activity' BIOCHEMICAL AND BIOPHYSICAL COMMUNICATIONS, vol. 252, 1998, pages 190-194, XP002100108
 - D5: BOEHM T ET AL: 'Disruption of the KEX1 gene in Pichia pastoris allows expression of full-length murine and human endostatin' YEAST, vol. 15, 1999. pages 563-572, XP002109421
- 2. Novelty and Inventive step (Article 33(2) and (3) PCT)
 - The present application discloses methods for the recombinant production of Endostatin[™] (claims 1-10) as well as methods for purifying Endostatin[™] (claims 11-23), leading to large scale recovery of the protein.
- 2.1. D1 discloses the recombinant expression of human Endostatin in cells transduced with constructs having 100% identity with SEQ ID Nos:3, 4, 5, 6, 8 and 11 (Examples 1-4). D1 is thus detrimental to the novelty and inventive step of claims 1 and 5-7.
- 2.2. D2 discloses the chromatographic isolation of Endostatin proteins from human blood ultrafiltrate through cation exchange and RP chromatography and the subsequent

EXAMINATION REPORT - SEPARATE SHEET

lyophilisation of aliquots. Recombinant endostatin can be produced by e.g. Pichia pastoris, E. coli, baculovirus or human embryonic kidney cells. D2 is thus detrimental to the novelty and inventive step of claims 1-8.

- 2.3. D3-D5 disclose the recombinant production of murine Endostatin in *Pichia pastoris* and its subsequent purification. D3-D5 are thus detrimental to the novelty and/or inventive step of claims 1 and 3-10.
- 3. Industrial applicability (Article 33(4) PCT) The subject-matter of the present set of claims appears to be industrially applicable under the terms of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(ii) PCT, documents D1-D5 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.